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14. ABSTRACT
Conventional chemotherapy with cell killing en mass often targets mitotic cells with less specificity, which likely leads to undesirable side effect. Knowing specific molecular defects in cancer cells has led to discover new chemotherapeutic agents. Thus, combined agents targeting different defected pathways in cancer cells have a better chance to eradicate tumor completely. Thus, to achieve a cure, a comprehensive targeting strategy needs to be implemented. In addition, improved methods for monitoring drug delivery and tumor response in a nearly real-time manner should offer a safe and effective treatment. This project carried out by a team of chemist, radiologist, and molecular tumor biologist is to develop a novel drug delivery system with new small molecular therapeutic agents assisted with new imaging probe is expect to bring a new frontier for prostate cancer management. Our objective is to develop dendrimer-based theranostic agent with prostate cancer specificity and positron emission tomography imaging capability that can prevent the early onset of PCa metastasis or delay the progression of metastasis. The mission of my project is to design small peptide derived from tumor suppressor DAB2 family as therapeutic agent and examine its biology activities.

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INTRODUCTION

Metastatic castration-resistant prostate cancer (CRPC) is considered as the lethal phenotype of this disease. With the advances of molecular biologic and genomic technologies, more detailed molecular mechanisms of the development of CRPC have been reported. Many studies (1, 2) demonstrate that epithelial-to-mesenchymal transition (EMT) play an important role in the initial stage of cancer metastasis and the onset of CRPC. It appears that CRPC exhibits many similar phenotypes of prostate stem cell (3-5), suggesting that a clonal expansion of small prostate cancer stem cell (PCSC) population from the original tumor and/or de-differentiation of prostate cancer lead to PCSC. It is also believed that cancer stem cell (CSC) can drive tumor population expansion and relapse after many forms of therapy through chemo-resistance (6, 7) since CSC are more resistant to apoptosis induced by chemotherapy, with high expression of anti-apoptotic molecules and reduced expression of pro-apoptotic genes (8). Thus, new therapeutic strategy is needed for targeting CSC in order to eradicate CRPC.

This project combines the recent advances in CRPC research from three different laboratories to develop a new molecular medicine. The goal of this project is to construct dendrimer nanoconjuate containing a prostate specific cell permeation peptide, peptide therapeutic(s) and bifunctional chelator for PET imaging. Dr. Simanek's laboratory will make dendrimers that bear functional handles for conjugation with imaging agents (from Dr. Sun's laboratory) and proline-rich peptide as a therapeutic agent (from my laboratory).

BODY

Based on the screening results of small peptide from 6 different CRPC lines from Year 1, Dr. Simanek has constructed a variety of dendrimer unit and conjugated with small peptide candidates identified from Year 1. Using these compounds, we have validated the activities and specificities of these peptides. Currently, Dr. Sun is adding imaging tracer onto dendrimer in order to complete theranostic agent for animal testing.

Aim 2: To select potent compounds with screening systems based on specific mechanism(s) of action.

Task 3 (Months 13– 24) Validation of the activities of dendrimer-conjugated therapeutic peptides.

In this year, we made new design by conjugating R11 targeting peptide and P10 therapeutic peptide separately with dendrimer unit. We further tested the biologic activity of these compounds in a highly aggressive PCa cell line (LAPC4-KD). As shown in Fig. 1A, the treatment of CSIV-81 (with R11 and P10) with cells is able to inhibit Akt activation. In contrast, the treatment of control compound (CSIV-78 or CSV-88) or solvent (DMSO) into cells did not have any effect on Akt activation. Furthermore, we showed that cell morphology and cell number were altered in the presence of CSIV-81 but not control compound significantly (Fig. 1B). In addition, using live cell assay (i.e, MTT), CSIV-81 was able to significantly inhibit cell growth compared with DMSO

control or CSIV-78 (Fig. 1C). Nevertheless, the biologic activities of CSIV-81 indicate that individual R11 and P10 are still functional

We expect to start in vivo studies such as bio-distribution, pharmacokinetics, and therapeutic efficacy starting Year 3.

KEY RESEARCH ACCOMPLISHMENTS

- Validate the activitities of dendrimer-conjugated peptides.

- Publish 1 manuscript to discuss the need of personalized therapy for castration-resistant prostate cancer.

REPORTABLE OUTCOMES

- Liu, H.H., Tsai, Y.S., Lai, C.L., Tang, C.H., Lai, C.H., Wu, H.C., Hsieh, J.T., Yang, C.R. (2014) Evolving avenue of personalized therapy for castration-resistant prostate cancer. BIoMed., 4:e7-15.

CONCLUSION

In the second year, we have validated the activities of dendrimer-conjugated therapeutic peptides; the activities of majority of peptides remain the same. However, we did not observe any enhancement of activity after dendrimer conjugation.

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Appendices

Figure 1 The activities of dendrimer-PR peptide in PCa cells. (A) Cells were treated with 50 mM of peptide 30 min and cell lysates were harvested and subjected to western blot analyses. (B) The morphologic change of cells was photographed 24 hrs after treatment. (C) The concentration effect of compounds on cell growth.